

FORM PTO-1390 (Modified) (REV 10-95)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				00537/161002
INTERNATIONAL APPLICATION NO. PCT/EP98/02999		INTERNATIONAL FILING DATE 13 May 1998 (13.05.1998)		U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 09/423684
TITLE OF INVENTION <b>SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING BODY WEIGHT</b>		PRIORITY DATE CLAIMED 13 May 1997 (13.05.1997)		
APPLICANT(S) FOR DO/EO/US <b>Michael Anthony CAWTHORNE, Yong-Ling LIU, Matthew V. SENNITT</b>				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371 (c) (2))             <ol style="list-style-type: none"> <li>a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</li> <li>7. <input type="checkbox"/> A copy of the International Search Report (PCT/ISA/210).</li> <li>8. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))             <ol style="list-style-type: none"> <li>a. <input checked="" type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input checked="" type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li>9. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>10. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).</li> <li>11. <input checked="" type="checkbox"/> A copy of the International Preliminary Examination Report (PCT/IPEA/409).</li> <li>12. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).</li> </ol>				
Items 13 to 18 below concern document(s) or information included:				
<ol style="list-style-type: none"> <li>13. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>14. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>15. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</li> <li><b>A SECOND or SUBSEQUENT</b> preliminary amendment.</li> <li>16. <input type="checkbox"/> A substitute specification.</li> <li>17. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>18. <input checked="" type="checkbox"/> Certificate of Mailing by Express Mail</li> <li>19. <input type="checkbox"/> Other items or information:</li> </ol>				
<p>"Express Mail" label number: EL445347119US          Date of Deposit : <u>November 10 1999</u>          I hereby certify that under 37 CFR 1.10 that this correspondence is being deposited          with the United States Postal Service as "Express Mail Post Office To Addressee"          with sufficient postage on the date indicated above and is addressed to the Assistant          Commissioner for Patents, Washington, D.C. 20231.</p> <p><u>R. Tanabbaum</u></p>				

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR <b>09/1423684</b>	INTERNATIONAL APPLICATION NO. PCT/EP98/02999	ATTORNEY'S DOCKET NUMBER 00537/161002
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20. The following fees are submitted:

**BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :**

<input checked="" type="checkbox"/> Search Report has been prepared by the EPO or JPO .....	\$840.00
<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) .....	\$670.00
<input type="checkbox"/> No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .....	\$760.00
<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....	\$970.00
<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....	\$96.00

**CALCULATIONS PTO USE ONLY****ENTER APPROPRIATE BASIC FEE AMOUNT =**

\$840.00

Surcharge of \$130.00 for furnishing the oath or declaration later than  20  30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

\$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	60 - 20 =	40	x \$22.00	\$880.00
Independent claims	4 - 3 =	1	x \$82.00	\$82.00
Multiple Dependent Claims (check if applicable).			☒	\$260.00

**TOTAL OF ABOVE CALCULATIONS = \$2,062.00**

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).

\$0.00

**SUBTOTAL = \$2,062.00**Processing fee of \$130.00 for furnishing the English translation later than  20  30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$0.00

**TOTAL NATIONAL FEE = \$2,062.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

\$0.00

**TOTAL FEES ENCLOSED = \$2,062.00**

	Amount to be: refunded	\$
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 A check in the amount of **\$2,062.00** to cover the above fees is enclosed. Please charge my Deposit Account No. in the amount of to cover the above fees. A duplicate copy of this sheet is enclosed. The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **06-1050** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Y. Rocky Tsao  
Fish & Richardson PC  
225 Franklin Street  
Boston, Massachusetts 02110

*Y. Rocky Tsao*

SIGNATURE

Y. Rocky Tsao

NAME

34,053

REGISTRATION NUMBER

*11-10-99*

DATE

420 Rec'd PCT/PTO 10 NOV 1999

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Michael Anthony Cawthorne  
et al.Art Unit : Unknown  
Examiner : Unknown

Serial No. :

Filed : November 10, 1999

Title : SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING  
BODY WEIGHTAssistant Commissioner for Patents  
Washington, D.C. 20231PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Specification:

Page 1, before the first line, please insert the following paragraph: --This is a continuation of International Patent Application No. PCT/EP98/02999, with an international filing date of 13 May 1998, now pending, which is a continuation of U.S. Patent Application No. 08/854,941, with a filing date of 13 May 1997, now abandoned.--

In the Claims:

Delete claim 37.

REMARKS

The specification is amended to recite claimed benefit under 35 USC 120 from International Patent Application PCT/EP98/02999 and its corresponding US application.

No new matter has been added by the above amendment.

## CERTIFICATE OF MAILING BY EXPRESS MAIL

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I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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F. Tawenbaum

Typed or Printed Name of Person Signing Certificate

Claims 1-36 are now pending. Prompt examination of the present application, as amended, is respectfully requested.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 11-9-99

Y. Rocky Tsao

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Reg. No. 34,053

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20003417.doc

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**SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING BODY WEIGHT**

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5 This invention relates to a method and composition useful for reducing body weight in human or mammalian animal bodies.

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**BACKGROUND OF THE INVENTION**

10 An estimated 35 million Americans are at least 20% overweight (Biotechnology 13:1060-1063 (1995)), a level at which health risks are significantly elevated. Nearly twice this number of Americans believe themselves to be overweight. A comparable picture is reported elsewhere.

15 For example, in the United Kingdom, approximately one third of the women and 43% of the men are overweight, with at least one in six women and one in eight men classifiable as medically obese (Purnell, S., Highfield, The Daily Telegraph, Sept. 30, 1995). There, therefore, 20 are both aesthetic and health reasons for weight control.

In the medically obese population, the condition is more severe and often associated with a myriad of serious medical problems such as non-insulin dependent diabetes mellitus, hypertension, dyslipidemia, coronary 25 heart disease and musculoskeletal disorders. Thus, obesity is not just a problem of passive increase in adipose mass. It has been suggested that the underlying metabolic alterations in obesity may be amenable to therapeutic intervention (Goldstein, D.J., et al., Am. J. 30 Clin. Nutr., 60:647-657 (1994)).

SUMMARY OF THE INVENTION

The present invention relates to a method of decreasing body weight in a patient (e.g., a mammal such as a human). The method includes the step of 5 administering a therapeutically effective amount of somatostatin or a somatostatin agonist to said patient. The somatostatin or somatostatin agonist may be administered parenterally, e.g., administered intravenously, subcutaneously, or by implantation of a 10 sustained release formulation. In one embodiment, the patient is obese (e.g., as defined by either 20-25% over normal body weight (Statistical Bulletin, Metropolitan Life Insurance Co., Vol. 40, pg. 1 (1959) or as defined by body mass index (BMI) greater than 25% over normal and 15 including risk factors or a BMI greater than 30% over normal (see, e.g., Bray, GA and Gray, DS, Diabetes/Metabolism Review 4:653-679 (1988); Flynn, et al., Proc. Nutritional Society 50:413 (1991)). In another embodiment, the patient is a non-insulin 20 dependent diabetic (i.e., type-2 diabetic).

The invention also comprises a pharmaceutical or cosmetic composition comprising a somatostatin or a somatostatin agonist. It further comprises the use of such compositions in the preparation of a pharmaceutical 25 or cosmetic composition for the reduction of excessive body weight in a human or mammalian animal.

The term "somatostatin agonist" will be defined below. A therapeutically effective amount depends upon the condition being treated, the route of administration 30 chosen, and the specific activity of the compound used

and ultimately will be decided by the attending physician or veterinarian (e.g., between 5  $\mu$ g/day to 5 mg/day). In one embodiment, the somatostatin agonist is administered to the patient until the patient has lost the requisite 5 amount of body weight (e.g., the patient is no longer medically obese). In another embodiment, the somatostatin agonist is administered for the lifetime of the patient (e.g., maintaining normal body weight or secondary endpoints). In another embodiment, the 10 somatostatin agonist is administered for cosmetic purposes.

The somatostatin agonist may be injected parenterally, e.g., intravenously, into the bloodstream of the subject being treated. However, it will be 15 readily appreciated by those skilled in the art that the route, such as intravenous, subcutaneous, intramuscular, intraperitoneal, enterally, transdermally, transmucosally, sustained released polymer compositions (e.g., a lactic acid polymer or copolymer microparticle or implant), profusion, nasal, oral, etc., will vary with the 20 condition being treated and the activity and bioavailability of the somatostatin agonist being used.

While it is possible for the somatostatin agonist to be administered as the pure or substantially pure 25 compound, it may also be presented as a pharmaceutical formulation or preparation. The formulations to be used in the present invention, for both humans and animals, comprise any of the somatostatin agonists to be described below, together with one or more pharmaceutically

acceptable carriers thereof, and optionally other therapeutic ingredients.

The carrier must be "acceptable" in the sense of being compatible with the active ingredient(s) of the formulation (e.g., capable of stabilizing peptides) and not deleterious to the subject to be treated. Desirably, the formulation should not include oxidizing agents or other substances with which peptides are known to be incompatible. For example, somatostatin agonists in the cyclized form (e.g., internal cysteine disulfide bond) are oxidized; thus, the presence of reducing agents as excipients could lead to an opening of the cysteine disulfide bridge. On the other hand, highly oxidative conditions can lead to the formation of cysteine sulfoxide and to the oxidation of tryptophan. Consequently, it is important to carefully select the excipient. pH is another key factor, and it may be necessary to buffer the product under slightly acidic conditions (pH 5 to 6).

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier which constitutes one or more accessory ingredients.

In general, the formulations for tablets or powders are prepared by uniformly and intimately blending the active ingredient with finely divided solid carriers, and then, if necessary, as in the case of tablets, forming the product into the desired shape and size.

Formulations suitable for parenteral (e.g., intravenous) administration, on the other hand, conveniently comprise sterile aqueous solutions of the active ingredient(s). Preferably, the solutions are isotonic with the blood of the subject to be treated. Such formulations may be conveniently prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering said solution sterile. The formulation may be presented in unit or multi-dose containers, for example, sealed ampoules or vials.

Formulations suitable for sustained release parenteral administrations (e.g., biodegradable polymer formulations such as polyesters containing lactic or glycolic acid residues) are also well known in the art. See, e.g., U.S. Patent Nos. 3,773,919 and 4,767,628 and PCT Publication No. WO 94/15587.

The somatostatin or somatostatin agonist may also be administered with other antiobesity agents such as phentermine, diethylpropion, methamphetamine, phendimetrazine, phenmetrazine, diethylpropion, phentermine, mazindol, dextroamphetamine, phentermine, bezphetamine, orlistat,  $\beta$ 3-adrenergic agonists (e.g., BTA-234 and SR58611A), sibutramine, phenylpropanolamine, dexfenfetamine, leptin, or bromocriptine.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments and from the claims.

Abbreviations

$\beta$ -Nal =  $\beta$ -naphthylalanine

$\beta$ -Pal =  $\beta$ -pyridylalanine

5 hArg(Bu) = N-guanidino- $\beta$ -butyl)-homoarginine

hArg(Et)<sub>2</sub> = N, N'-guanidino-(dimethyl)-homoarginine

hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub> = N, N'-guanidino-bis-(2,2,2,-trifluoroethyl) - homoarginine

hArg(CH<sub>3</sub>, hexyl) = N, N'-guanidino-(methyl, hexyl) -

10 homoarginine

Lys(Me) = N-methyllysine

Lys(iPr) = N-isopropyllysine

AmPhe = aminomethylphenylalanine

AChxAla = aminocyclohexylalanine

15 Abu =  $\alpha$ -aminobutyric acid

Tpo = 4-thiaproline

MeLeu = N-methylleucine

Orn = ornithine

Nle = norleucine

20 Nva = norvaline

Trp(Br) = 5-bromo-tryptophan

Trp(F) = 5-fluoro-tryptophan

Trp(NO<sub>2</sub>) = 5-nitro-tryptophan

Gaba =  $\gamma$ -aminobutyric acid

25 Bmp =  $\beta$ -mercaptopropionyl

Ac = acetyl

Pen = pencillamine

DETAILED DESCRIPTION OF THE INVENTION

30 It is believed that one skilled in the art can, based on the description herein, utilize the present

invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

5 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents, and other references  
10 mentioned herein are incorporated by reference.

Somatostatin and its Agonists

Somatostatin (somatotropin release inhibiting factor or SRIF) has both a 14 amino acid isoform (somatostatin-14) and a 28 amino acid isoform (somatostatin-28). See Wilson, J. & Foster, D., *Williams Textbook of Endocrinology*, p. 510 (7th ed., 1985). The compound is an inhibitor of secretion of the growth hormone and was originally isolated from the  
20 hypothalamus. Brazeau, et al., *Science* 179:77 (1973). Native somatostatin has a very short duration of effect in vivo since it is rapidly inactivated by endo- and exopeptidase. Many novel analogs have been prepared in order to enhance the duration of effect, biological  
25 activity, and selectivity (e.g., for the particular somatostatin receptor) of this hormone. Such analogs will be called "somatostatin agonists" herein.

Various somatostatin receptors (SSTRs) have been isolated, e.g., SSTR-1, SSTR-2, SSTR-3, SSTR-4, and SSTR-  
30 5. Thus, the somatostatin agonist may be a SSTR-1

agonist, SSTR-2 agonist, SSTR-3 agonist, SSTR-4 agonist or an SSTR-5 agonist. In one embodiment, the somatostatin agonist of the present invention is an SSTR-5 agonist or an SSTR-2 agonist. What is meant by an "SSTR-5 agonist" or an "SSTR-2 agonist" is a compound which (1) has a high affinity (e.g.,  $K_i$  of less than 1  $\mu\text{M}$  or, preferably, of less than 10 nM, or less than 2 nM, or of less than 1 nM) for the SSTR-5 or SSTR-2, respectively (e.g., as defined by the receptor binding assay described below), and (2) decreases body weight of a patient (e.g., as defined by the biological assay described below). The somatostatin agonist may also be selective for a particular somatostatin receptor, e.g., have a higher binding affinity for a particular somatostatin receptor subtype as compared to the other receptor subtypes. In one embodiment, the somatostatin receptor is an SSTR-5 selective agonist or SSTR-2 selective agonist. What is meant by an SSTR-5 selective agonist is a somatostatin agonist which (1) has a higher binding affinity (i.e.,  $K_i$ ) for SSTR-5 than for either SSTR-1, SSTR-2, SSTR-3, or SSTR-4 and (2) decreases body weight of a patient (e.g., as defined by the biological assay described below). In one embodiment, the SSTR-5 selective agonist has a  $K_i$  for SSTR-5 that is at least 2 times (e.g., at least 5 times or at least 10 times) less than its  $K_i$  for the SSTR-2 receptor (e.g., as defined by the receptor binding assay described below).

Somatostatin agonists which can be used to practice the therapeutic method of the present invention include, but are not limited to, those covered by

formulae or those specifically recited in the publications set forth below, all of which are hereby incorporated by reference.

EP Application No. P5 164 EU (Inventor: G. Keri);  
5 Van Binst, G. et al. Peptide Research 5:8 (1992);  
Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having Antitumor Activity", 22nd European peptide Symposium, September 13-19, 1992, Interlaken, Switzerland;

10 PCT Application WO 91/09056 (1991);  
EP Application 0 363 589 A2 (1990);  
U.S. Patent No. 4,904,642 (1990);  
U.S. Patent No. 4,871,717 (1989);  
U.S. Patent No. 4,853,371 (1989);  
15 U.S. Patent No. 4,725,577 (1988);  
U.S. Patent No. 4,684,620 (1987);  
U.S. Patent No. 4,650,787 (1987);  
U.S. Patent No. 4,603,120 (1986);  
U.S. Patent No. 4,585,755 (1986);  
20 EP Application 0 203 031 A2 (1986);  
U.S. Patent No. 4,522,813 (1985);  
U.S. Patent No. 4,486,415 (1984);  
U.S. Patent No. 4,485,101 (1984);  
U.S. Patent No. 4,435,385 (1984);  
25 U.S. Patent No. 4,395,403 (1983);  
U.S. Patent No. 4,369,179 (1983);  
U.S. Patent No. 4,360,516 (1982);  
U.S. Patent No. 4,358,439 (1982);  
U.S. Patent No. 4,328,214 (1982);  
30 U.S. Patent No. 4,316,890 (1982);

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U.S. Patent No. 4,310,518 (1982);  
U.S. Patent No. 4,291,022 (1981);  
U.S. Patent No. 4,238,481 (1980);  
U.S. Patent No. 4,235,886 (1980);  
5 U.S. Patent No. 4,224,190 (1980);  
U.S. Patent No. 4,211,693 (1980);  
U.S. Patent No. 4,190,648 (1980);  
U.S. Patent No. 4,146,612 (1979);  
U.S. Patent No. 4,133,782 (1979);  
10 U.S. Patent No. 5,506,339 (1996);  
U.S. Patent No. 4,261,885 (1981);  
U.S. Patent No. 4,728,638 (1988);  
U.S. Patent No. 4,282,143 (1981);  
U.S. Patent No. 4,215,039 (1980);  
U.S. Patent No. 4,209,426 (1980);  
15 U.S. Patent No. 4,190,575 (1980);  
EP Patent No. 0 389 180 (1990);  
EP Application No. 0 505 680 (1982);  
EP Application No. 0 083 305 (1982);  
EP Application No. 0 030 920 (1980);  
20 PCT Application No. WO 88/05052 (1988);  
PCT Application No. WO 90/12811 (1990);  
PCT Application No. WO 97/01579 (1997);  
PCT Application No. WO 91/18016 (1991);  
25 U.K. Application No. GB 2,095,261 (1981); and  
French Application No. FR 2,522,655 (1983).

Examples of somatostatin agonists include, but are not limited to, the following somatostatin analogs which are disclosed in the above-cited references:

30 H-D- $\beta$ -Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub> (BIM-23014);

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys- $\beta$ -Nal-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys- $\beta$ -Nal-NH<sub>2</sub>;  
H-D- $\beta$ -Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH;  
H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;  
H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH;  
H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH;  
H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;  
H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol (Octreotide);  
H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
Ac-D-Phe-Lys-Tyr-D-Trp-Lys-Val-Asp-Thr-NH<sub>2</sub> (an amide  
bridge formed between Lys and Asp);  
Ac-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
20 Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
Ac-D-hArg(Et)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
Ac-L-hArg(Et)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
25 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>;  
Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-  
NHEt;

12

Ac-L-hArg(CH<sub>2</sub>-CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NH<sub>2</sub>;

5 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NHET;

Ac-hArg(CH<sub>3</sub>, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

H-hArg(hexyl<sub>2</sub>)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

10 Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHET;

Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>;

Propionyl-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-Thr-NH<sub>2</sub>;

15 Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg(Et)<sub>2</sub>-NH<sub>2</sub>;

Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

20 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>;

Ac-D-hArg(Et)<sub>2</sub>-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH<sub>2</sub>;

25 H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH<sub>2</sub>;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH<sub>2</sub>;

H-Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>;

H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;

30 H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys- $\beta$ -Nal-NH<sub>2</sub>;  
H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
Ac-D- $\beta$ -Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-  
NH<sub>2</sub>;

5 H-D- $\beta$ -Nal-Cys-Tyr-D-Trp-Lys-Val-Cys- $\beta$ -Nal-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys- $\beta$ -Nal-NH<sub>2</sub>;  
H-D- $\beta$ -Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;  
H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;  
Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;

10 H-D-Phe-Cys- $\beta$ -Nal-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH<sub>2</sub>;  
cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe);

15 cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe);  
cyclo(Pro-Tyr-D-Trp-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe);  
cyclo(Pro-Phe-L-Trp-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp(F)-Lys-Thr-Phe);

20 cyclo(Pro-Phe-Trp(F)-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Ser-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe);  
cyclo(D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe);  
cyclo(D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe);

25 cyclo(D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe);  
cyclo(D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr);  
cyclo(Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe);  
cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe);

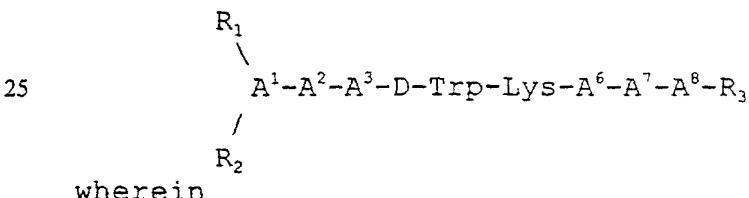
14

cyclo(N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);  
cyclo(Pro-Tyr-D-Trp-t-Amphe-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-t-Amphe-Thr-Phe);  
cyclo(N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe);  
5 cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba);  
cyclo(Asn-Phe-D-Trp-Lys-Thr-Phe);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-NH(CH<sub>2</sub>)<sub>4</sub>CO);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala);  
10 cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH;  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe);  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);  
15 cyclo(Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp(NO<sub>2</sub>)-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-Trp(Br)-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe(I)-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr(But)-Gaba);  
20 cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-  
Cys)-OH;  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-  
Cys)-OH;  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-  
25 Cys)-OH;  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-  
Cys)-OH;  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba);  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba);  
30 cyclo(Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba);

cyclo(Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-(CH<sub>2</sub>)<sub>3</sub>-CO);  
 cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
 cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
 cyclo(Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
 5 H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub> (BIM-23268);  
 H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH<sub>2</sub> (BIM-23284);  
 H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub> (BIM-23295); and  
 H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub> (BIM-23313).

Note that for all somatostatin agonists described  
 10 herein, each amino acid residue represents the structure  
 of -NH-C(R)H-CO-, in which R is the side chain (e.g., CH<sub>3</sub>  
 for Ala) except for Thr-ol which means -NH-CH(CH(CH<sub>3</sub>)OH)-  
 CH<sub>2</sub>-OH and Pro which means prolinyl. Lines between amino  
 acid residues represent peptide bonds which join the  
 15 amino acids. Also, where the amino acid residue is  
 optically active, it is the L-form configuration that is  
 intended unless D-form is expressly designated. A  
 disulfide bridge is formed between the two free thiols  
 (e.g., Cys, Pen, or Bmp residues); however, it is not  
 20 shown.

Use of linear somatostatin agonists of the  
 following formula is also within the invention:



A<sup>1</sup> is a D- or L- isomer of Ala, Leu, Ile, Val,  
 30 Nle, Thr, Ser,  $\beta$ -Nal,  $\beta$ -Pal, Trp, Phe, 2,4-dichloro-Phe,  
 pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH<sub>3</sub>,  
 Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

$A^2$  is Ala, Leu, Ile, Val, Nle, Phe,  $\beta$ -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe,  $\alpha$ -X-Phe, or  $p$ -X-Phe, wherein X is  $CH_3$ , Cl, Br, F, OH,  $OCH_3$  or  $NO_2$ ;

5  $A^3$  is pyridyl-Ala, Trp, Phe,  $\beta$ -Nal, 2,4-dichloro-Phe, pentafluoro-Phe,  $\alpha$ -X-Phe, or  $p$ -X-Phe, wherein X is  $CH_3$ , Cl, Br, F, OH,  $OCH_3$  or  $NO_2$ ;

$A^6$  is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

10  $A^7$  is Ala, Leu, Ile, Val, Nle, Phe,  $\beta$ -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe,  $\alpha$ -X-Phe, or  $p$ -X-Phe, wherein X is  $CH_3$ , Cl, Br, F, OH,  $OCH_3$  or  $NO_2$ ;

15  $A^8$  is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe,  $\beta$ -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe,  $p$ -X-Phe, or  $\alpha$ -X-Phe, wherein X is  $CH_3$ , Cl, Br, F, OH,  $OCH_3$  or  $NO_2$ ;

20 each  $R_1$  and  $R_2$ , independently, is H, lower acyl or lower alkyl; and  $R_3$  is OH or  $NH_2$ ; provided that at least one of  $A^1$  and  $A^8$  and one of  $A^2$  and  $A^7$  must be an aromatic amino acid; and further provided that  $A^1$ ,  $A^2$ ,  $A^7$  and  $A^8$  cannot all be aromatic amino acids.

Examples of linear agonists to be used in the method of this invention include:

25 H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>;

H-D-Phe-p-NO<sub>2</sub>-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub> (BIM-23052);

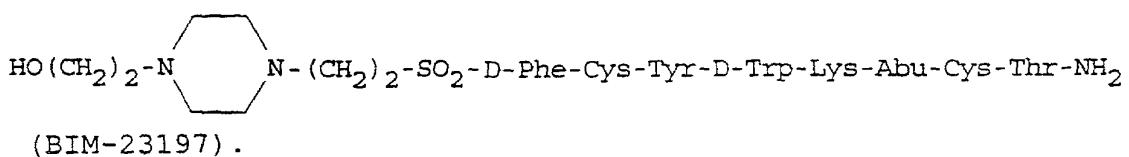
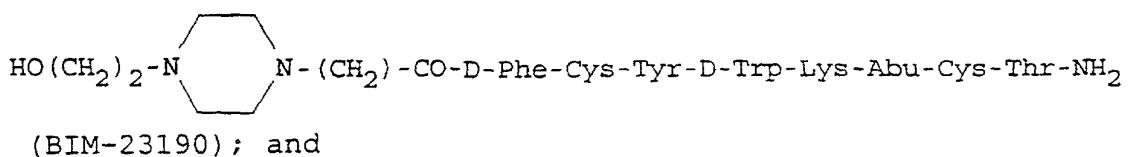
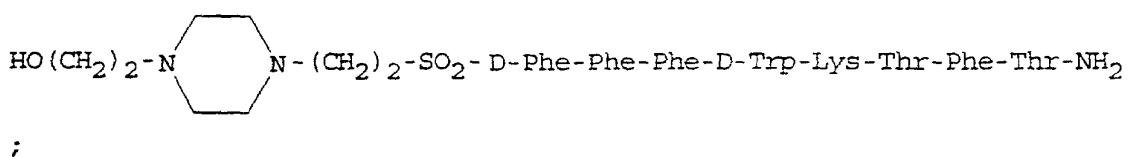
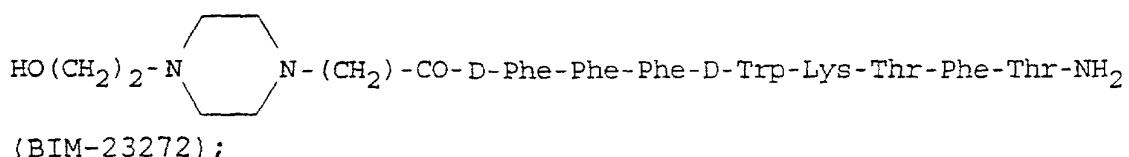
H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

30 and

H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala- $\beta$ -D-Nal-NH<sub>2</sub>.

If desired, one or more chemical moieties, e.g., a sugar derivative, mono or poly-hydroxy C<sub>2-12</sub> alkyl, mono or poly-hydroxy C<sub>2-12</sub> acyl groups, or a piperazine derivative, can be attached to the somatostatin agonist, e.g., to the N-terminus amino acid. See PCT Application WO 88/02756, European Application 0 329 295, and PCT Application No. WO 94/04752. An example of a somatostatin agonists which contain N-terminal chemical substitutions are:



Synthesis of somatostatin agonists

The methods for synthesizing somatostatin agonists is well documented and are within the ability of a person of ordinary skill in the art.

Synthesis of short amino acid sequences is well established in the peptide art. For example, synthesis of H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>, described above, can be achieved by following the protocol set forth in Example I of European Patent Application 0 395 417 A1. The synthesis of somatostatin agonists with a substituted N-terminus can be achieved, for example, by following the protocol set forth in WO 88/02756, European Patent Application No. 0 329 295, and PCT Publication No. 10 WO 94/04752.

#### Somatostatin Receptor Binding Assays

The human SSTR-1, SSTR-2, SSTR-3, SSTR-4, and SSTR-5 cDNA clones have been described (SSTR-1 and SSTR-2 in Yamada, Y., et al., Proc. Natl. Acad. Sci. USA, 89:251-255 (1992); SSTR-3 in Yamada, et al., Mol. Endocrinol. 6:2136-2142 (1993); and SSTR-4 and SSTR-5 in Yamada, et al., Biochem. Biophys. Res. Commun. 195:844-852 (1993)) and are also available from American Type 20 Culture Collection (ATCC, Rockville, MD) (ATCC Nos. 79044 (SSTR-1), 79046 (SSTR-2), and 79048 (SSTR-3)). Based on the restriction endonuclease maps, the entire coding region of each SSTR cDNA may be excised by suitable restriction endonuclease digestion (Maniatis, T., et al., 25 *Molecular Cloning - A Laboratory Manual*, CSHL, 1982). Restriction endonucleases are available from New England Biolabs (Beverly, MA). This cDNA fragment was inserted into the mammalian expression vector, pCMV (Russell, D., et al., J. Biol. Chem., 264:8222-8229 (1989)), using 30 standard molecular biology techniques (see e.g.,

Maniatis, T., et al., Molecular Cloning,-A Laboratory Manual, Cold Spring Harbor Laboratory, 1982) to produce the expression plasmid, pCMV-human SSTR-1 through pCMV-human SSTR-5. Other mammalian expression vectors include 5 pcDNA1/Amp (Invitrogen, Sandlesy, CA). The expression plasmids were introduced into the suitable bacterial host, E. Coli HB101 (Stratagene, La Jolla, CA) and plasmid DNAs, for transfection, were prepared on Cesium Chloride gradients.

10 CHO-K1 (ovary, Chinese hamster) cells were obtained from ATCC (ATCC No. CCL 61). The cells were grown and maintained in Ham's F12 media (Gibco BRL, Grand Island, NY) supplemented with 10% fetal bovine serum under standard tissue culture conditions. For 15 transfection, the cells were seeded at a density 1 x 10<sup>6</sup>/60-cm plate (Baxter Scientific Products, McGaw Park, IL.). DNA mediated transfection was carried out using the calcium phosphate co-precipitation method (Ausubel, F.M., et al., Current Protocols in Molecular Biology, 20 John Wiley & Sons, 1987). The plasmid pRSV-neo (ATCC; ATCC No. 37198) was included as a selectable marker at 1/10 the concentration of the expression plasmid. CHO-K1 25 clonal cell lines that have stably inherited the transfected DNA were selected for growth in Ham's F12 media containing 10% fetal bovine serum and 0.5mg/ml of G418 (Sigma). The cells were ring-cloned and expanded in the same media for analysis.

30 Expression of the human SSTR-1 through SSTR-5 receptors in the CHO-K1 cells were detected by Northern blot analysis of total RNA prepared from the cells

(Sambrook, J.E., et al., Molecular Cloning - A Laboratory Manual, Ed. 2., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989) and by receptor binding using [<sup>125</sup>I-Tyr<sup>11</sup>]somatostatin-14 as a ligand. Transfected cell lines expressing the human SSTR receptors were clonally expanded in culture and used in the following SSTR binding protocol.

Crude membranes were prepared by homogenization of the transfected cells in 20 ml of ice-cold 50 mM Tris-HCl with a POLYTRON homogenizer (setting 6, 15 sec). Buffer was added to obtain a final volume of 40 ml, and the homogenate was centrifuged in a Sorval SS-34 rotor at 39,000 g for 10 min at 0-4°C. The resulting supernatant was decanted and discarded. The pellet was rehomogenized in ice-cold buffer, diluted, and centrifuged as before. The final pellet was resuspended in the 10 mM Tris HCl and held on ice for the receptor binding assay.

Aliquots of the membrane preparation were incubated for 30 min at 30°C with 0.05 nM [<sup>125</sup>I-Tyr<sup>11</sup>]somatostatin-14 (2000 Ci/mmol; Amersham Corp., Arlington Heights, IL) in 50 mM HEPES (pH 7.4) containing a test somatostatin agonist of various concentrations (e.g., 10<sup>-11</sup> to 10<sup>-6</sup>), 10 mg/ml bovine serum albumin (fraction V) (Sigma Chemical Co., St. Louis, MO), MgCl<sub>2</sub> (5 mM), Trasylol (200 KIU ml), bacitracin (0.02 mg/ml), and phenylmethylsulphonyl fluoride (0.02 mg/ml). The final assay volume was 0.3 ml. The incubations were terminated by rapid filtration through GF/C filters (pre-soaked in 0.3% polyethylenimine for 30 min) using a Brandel

filtration manifold. Each tube and filter were then washed three times with 5 ml aliquots of ice-cold buffer.

Specific binding was defined as the total [<sup>125</sup>I-  
Tyr<sup>11</sup>]SRIF-14 bound minus that bound in the presence of  
5 1000 nM. The Ki values for the tested somatostatin  
agonists were calculated by using the following formula:  
Ki = IC<sub>50</sub> / [1+(LC/LEC)] where IC<sub>50</sub> is the concentration of  
test somatostatin agonist required to inhibit 50 percent  
of the specific binding of the radioligand [<sup>125</sup>I-  
10 Tyr<sup>11</sup>]somatostatin-14, LC is the concentration of the  
radioligand (0.05 nM), and LEC is the equilibrium  
dissociation constant of the radioligand (0.16 nM). The  
Ki values (nm) for the tested somatostatin agonists are  
shown in Table I.

15

TABLE I

	hsSTR-1	hsSTR-2	hsSTR-3	hsSTR-4	hsSTR-5
Somatostatin-14	2.26	0.23	1.2	1.8	1.41
Somatostatin-28	2.38	0.30	1.3	7.93	0.4
Octreotide	875	0.57	26.8	5029	6.78
BIM-23014	2414	0.75	97.9	1826	5.21
BIM-23052	97.6	11.96	5.6	127	1.22
BIM-23190	9120	0.35	215	7537	11.1
BIM-23197	6016	0.19	26.8	3897	9.81
BIM-23272	47.7	3.23	10.9	753	1.01
BIM-23284	27.9	19.3	35.6	58.6	0.85
BIM-23295	86.9	6.19	9.7	3.4	0.34
BIM-23313	15.1	4.78	25.5	55.3	0.30
BIM-26268	1227	15.06	545	3551	0.42

Weight Loss Studies

The effect of chronic (6 day) treatment with BIM-23268 on body weight gain/loss was examined in an obese animal model, the fatty (fa/fa) Zucker rats (purchased from Harlan-Olac, Bicester, Oxon, U.K. See Bray, G., Federation Proceedings 36:148-153 (1977). Eleven male fatty Zucker rats weighing about 450 grams were randomly divided into two groups, and their initial body weights recorded. The animals were housed in pairs in a normal 12 hour light:12 hour darkness cycle at  $20 \pm 2^\circ\text{C}$  and fed overnight *ad libitum*.

For the group assigned to receive drug treatment, the rats received the type-5 somatostatin receptor selective agonist BIM-23268C at 3 mg/kg, by subcutaneous injection twice a day at 10:00 a.m. and 5:00 p.m. The other group was treated with a subcutaneous injection of 0.1 ml/100 g of saline twice a day at 10:00 a.m. and 5:00 p.m. The animals were subjected to the BIM-23268 or saline treatment for a total of six days.

At 10:00 a.m. each day, food was removed and replaced with accurately weight 100 gram food pellet (a standard laboratory rat diet, Beekay rat and mouse diet, Bantin & Kingman, Hull, Humberside, U.K.). The amount of food remaining a 10:00 a.m. the next day was accurately weighed, recorded and replaced with 100 grams of fresh food pellets.

The animals were weighed each day during the 6-day treatment period at 5:00 p.m. The untreated control group mean weight was 414.09 at the start of the trial

and was 418.89 after six days. The BIM-23268 treated group's mean weight was 413.6 at the start of the trial and remained at 413.6 after six days. The average food consumption for the control group was 26.0 g/rat/day and 5 for the BIM-26268 group was 25.9 g/rat/day.

These results showed that body weight gain was lower in animals treated with BIM-23268. The effect on body weight change was not due to a toxic effect of the agent, as the treated group appeared healthy, and there 10 was no difference in the amount of food consumed over the entire treatment period.

#### Secondary Endpoints of Efficacy

Because of the amount of weight that must be lost 15 to achieve a clinically important alteration in risk for various sequelae of obesity, the Food and Drug Administration guidelines for the evaluation of weight-control drugs have recommended that additional endpoints showing a decrease in risk factors such as lipemia be 20 monitored.

Obese (fa/fa) Zucker rats were treated as in example 1 above. On the last day of treatment (day 6), food was removed at 5:00 p.m., and the rats were fasted overnight. At 9:00 a.m. the next day, the animals were 25 subjected to a glucose challenge, given as 0.8 gram/kg of glucose orally. Periodic 400  $\mu$ l of blood samples were taken from the tail vein (Peterson, R.G., ILAR News, 32:16-19 (1990)) 60 min. and 30 min. before and at 30, 60, 90, and 120 min. after the administration of the 30 glucose challenge (0.8 gram/kg orally). Aprotinin

(Traysylol, Bayer UK, Hayward's Health, W. Sussex, U.K.) and heparin (Sigma Chemical Co., Poole, Dorset, U.K.) were added to the blood samples to a final concentration of 400 KIU/ml and 100 units/ml, respectively. Plasma 5 fractions were prepared from these samples by centrifugation at 4000 x G in a microfuge, for the estimation of triglycerides and glycerol. Samples were then stored at -80°C until assayed.

Plasma glycerol and triglycerides were determined 10 using the Sigma Enzymatic (Tinder) calorimetric assay kit (Cat #337-B, Sigma Chemical Co., Poole, Dorset, U.K.) and measuring absorbance at 540 nm in a spectrophotometer.

After six days of treatment with BIM-23268C at 3 mg/kg twice a day by subcutaneous injection, both plasma 15 glycerol and triglycerides were significantly lowered, as exemplified by the samples taken at tim 30 and 60 minutes before the oral glucose challenge. See Fig. 1 and Fig.

2. The administration of an oral glucose challenge have no significant effect on plasma lipids. The BIM-23628C 20 treated group showed a significantly lower plasma glycerol and triglycerides throughout the 2-hour test period. The results suggested that BIM-23268C, following a 6-day treatment period at the prescribed dose was effective in reducing hypertriglyceridemia.

#### Assessment of Efficacy in Patient

The effect of the somatostatin agonist on obesity can be examined in patients by assessing total body weight, body mass index, total adipose tissue content, 30 subcutaneous tissue content, visceral adipose tissue

content (see, e.g., Zamboni, M., Amer. J. Clin. Nutr. 60:682-687 (1994). The effect of the somatostatin agonist can also be measured on other secondary endpoints, such as insulin sensitivity (see, e.g., 5 Bergman, R.N., et al., Endocrin. Rev. 6:45-86 (1985); Turner, R.C., Diabetes 44:1-10 (1995)), blood pressure (see, e.g., Maheux, P., Hypertension 24:695-698 (1994)), plasma lipids (see, e.g., Dubrey, S.W., et al., Diabetes 43:831-835 (1994)), and the other acceptable endpoints 10 recommended by the FDA Draft Guidelines for the Clinical Evaluation of Weight Control Drugs (1994) (see also, Drug & Market Development 6:36 (1994)).

#### OTHER EMBODIMENTS

15 The foregoing description has been limited to specific embodiments of this invention. It will be apparent, however, that variations and modifications may be made to the invention, with the attainment of some or all of the advantages of the invention. Such embodiments 20 are also within the scope of the following claims.

CLAIMS

1. A method of decreasing body weight in a patient, said method comprising administering a 5 therapeutically effective amount of somatostatin or a somatostatin agonist to said patient.

2. A method of claim 1, wherein said method comprises administering a therapeutically effective amount of a somatostatin agonist to said patient.

10 3. A method of claim 2, wherein said somatostatin agonist is a somatostatin type-2 receptor agonist.

4. A method of claim 2, wherein said somatostatin agonist is a somatostatin type-5 receptor agonist.

15 5. A method of claim 3, wherein said somatostatin type-2 receptor agonist has a  $K_i$  of less than 2 nM for the somatostatin type-2 receptor.

6. A method of claim 4, wherein said somatostatin type-5 receptor agonist has a  $K_i$  of less than 2 nM for the somatostatin type-5 receptor.

20 7. A method of claim 2, wherein said somatostatin agonist is a somatostatin type-2 receptor selective agonist.

8. A method of claim 2, wherein said somatostatin agonist is a somatostatin type-5 receptor selective 25 agonist.

9. A method of claim 7, wherein said somatostatin type-2 receptor selective agonist has a  $K_i$  for the somatostatin type-2 receptor that is at least 10 times less than the  $K_i$  for the somatostatin type-1, type-3, 30 type-4, and type-5 receptors.

10. A method of claim 8, wherein said somatostatin type-5 receptor selective agonist has a  $K_i$  for the somatostatin type-5 receptor that is at least 10 times less than the  $K_i$  for the somatostatin type-1, type-2, type-3, and type-4 receptors.

11. A method of decreasing body weight in a patient, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub>, wherein a disulfide bond exists between the free thiols of two Cys residues.

10 12. A method of claim 1, wherein said patient is an non-insulin-dependent diabetic human.

13. A method of claim 2, wherein said patient is an non-insulin-dependent diabetic human.

15 14. A method of claim 3, wherein said patient is an non-insulin-dependent diabetic human.

15 16. A method of claim 4, wherein said patient is an non-insulin-dependent diabetic human.

20 17. A method of claim 5, wherein said patient is an non-insulin-dependent diabetic human.

18. A method of claim 6, wherein said patient is an non-insulin-dependent diabetic human.

25 19. A method of claim 7, wherein said patient is an non-insulin-dependent diabetic human.

20 20. A method of claim 8, wherein said patient is an non-insulin-dependent diabetic human.

30 21. A method of claim 9, wherein said patient is an non-insulin-dependent diabetic human.

22. A method of claim 11, wherein said patient is an non-insulin-dependent diabetic human.

23. A method according to claim 1 wherein the somatostatin agonist is

- 5 H-D- $\beta$ -Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys- $\beta$ -Nal-NH<sub>2</sub>,
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys- $\beta$ -Nal-NH<sub>2</sub>,
- H-D- $\beta$ -Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub>,
- 10 H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub>,
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH,
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH,
- H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH,
- H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH,
- 15 H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH,
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,
- H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- 20 H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH<sub>2</sub>,
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,
- Ac-D-Phe-Lys\*-Tyr-D-Trp-Lys-Val-Asp-Thr-NH<sub>2</sub> (an amide bridge formed between Lys\* and Asp),
- 25 Ac-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- Ac-D-hArg(Et)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- Ac-L-hArg(Et)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,
- 30 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,

Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>,  
Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHET,  
Ac-L-hArg (CH<sub>2</sub>-CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
5 Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-  
NH<sub>2</sub>,  
Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-  
NHET,  
Ac-hArg (CH<sub>3</sub>, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
10 H-hArg (hexyl<sub>2</sub>)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
Ac-D-hArg (Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHET,  
Ac-D-hArg (Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>,  
Propionyl-D-hArg (Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-  
Thr-NH<sub>2</sub>,  
15 Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg (Et)<sub>2</sub>-  
NH<sub>2</sub>,  
Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-  
Thr-Cys-Thr-NH<sub>2</sub>,  
20 Ac-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-D-hArg (CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-  
Thr-Cys-Phe-NH<sub>2</sub>,  
Ac-D-hArg (Et)<sub>2</sub>-D-hArg (Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-  
Thr-NH<sub>2</sub>,  
25 Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-  
Cys-NH<sub>2</sub>,  
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,  
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH<sub>2</sub>,  
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH<sub>2</sub>,  
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>,  
30 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,

H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>,  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH<sub>2</sub>,  
H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,  
Ac-D-β-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,  
5 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>,  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>,  
H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>,  
H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>,  
Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>,  
10 H-D-Phe-Cys-β-Nal-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>,  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH<sub>2</sub>,  
cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe),  
cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe),  
cyclo(Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe),  
15 cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe),  
cyclo(Pro-Tyr-D-Trp-Lys-Thr-Phe),  
cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe),  
cyclo(Pro-Phe-L-Trp-Lys-Thr-Phe),  
cyclo(Pro-Phe-D-Trp(F)-Lys-Thr-Phe),  
20 cyclo(Pro-Phe-Trp(F)-Lys-Thr-Phe),  
cyclo(Pro-Phe-D-Trp-Lys-Ser-Phe),  
cyclo(Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe),  
cyclo(D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe),  
cyclo(D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe),  
25 cyclo(D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe),  
cyclo(D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr),  
cyclo(Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe),  
cyclo(Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe),  
cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe),

cyclo(N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe),  
cyclo(Pro-Tyr-D-Trp-4-Amphe-Thr-Phe),  
cyclo(Pro-Phe-D-Trp-4-Amphe-Thr-Phe),  
cyclo(N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe),  
5 cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba),  
cyclo(Asn-Phe-D-Trp-Lys-Thr-Phe),  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-NH(CH<sub>2</sub>)<sub>4</sub>CO),  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala),  
10 cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH,  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe),  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gly),  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly),  
15 cyclo(Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba),  
cyclo(Asn-Phe-Phe-D-Trp(NO<sub>2</sub>)-Lys-Thr-Phe-Gaba),  
cyclo(Asn-Phe-Phe-Trp(Br)-Lys-Thr-Phe-Gaba),  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe(I)-Gaba),  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr(But)-Gaba),  
20 cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-  
OH,  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-  
OH,  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-Cys)-  
25 OH,  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-  
Cys)-OH,  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba),  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba),  
30 cyclo(Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba),

cyclo(Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-(CH<sub>2</sub>)<sub>3</sub>-CO),

cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),

cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),

cyclo(Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba),

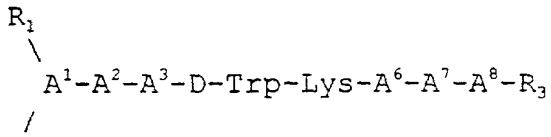
5 H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub>,

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH<sub>2</sub>,

H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub> or

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub>.

24. A method according to claim 1 wherein the  
10 somatostatin agonist is



15 wherein

A<sup>1</sup> is a D- or L- isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, β-Nal, β-Pal, Trp, Phe, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH<sub>3</sub>, 20 Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

A<sup>2</sup> is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

25 A<sup>3</sup> is pyridyl-Ala, Trp, Phe, β-Nal, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

A<sup>6</sup> is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

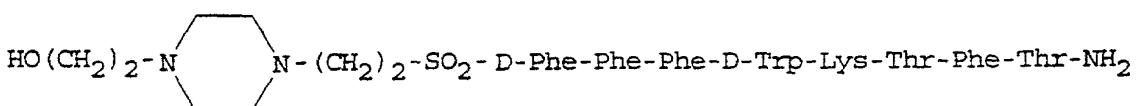
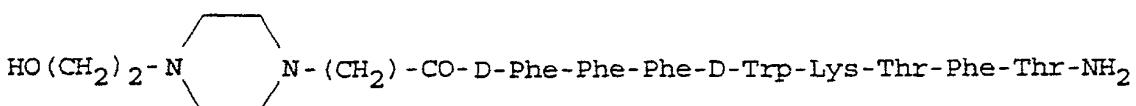
A<sup>7</sup> is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, 30 pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

$A^8$  is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe,  $\beta$ -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is  $CH_3$ , Cl, Br, F, OH,  $OCH_3$ , or  $NO_2$ ;

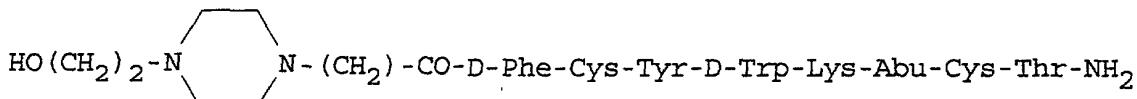
5 each  $R_1$  and  $R_2$ , independently, is H, lower acyl or lower alkyl; and  $R_3$  is OH or  $NH_2$ ; provided that at least one of  $A^1$  and  $A^8$  and one of  $A^2$  and  $A^7$  must be an aromatic amino acid; and further provided that  $A^1$ ,  $A^2$ ,  $A^7$  and  $A^8$  cannot all be aromatic amino acids.

10 25. A method according to claim 24 wherein the linear somatostatin agonist is  
 H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>,  
 H-D-Phe-p-NO<sub>2</sub>-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>,  
 H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>,  
 15 H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub> ,  
 H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>,  
 H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub> or  
 H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala- $\beta$ -D-Nal-NH<sub>2</sub>.

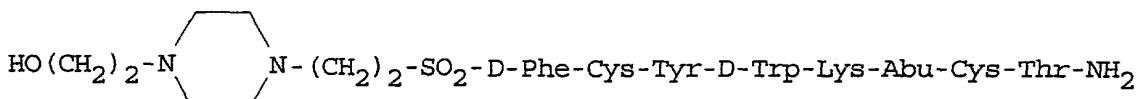
20 26. A method according to claim 1 wherein the somatostatin agonist is



M 26.07.99



or



5

27. A method according to claim 1 wherein said patient is obese.

10 28. A method according to claim 3 wherein said patient is obese.

29. A method according to claim 4 wherein said patient is obese.

15 30. A method according to claim 7 wherein said patient is obese.

31. A method according to claim 8 wherein said patient is obese.

32. A method according to claim 11 wherein said patient is obese.

20 33. A pharmaceutical or cosmetic composition comprising a therapeutically or cosmetically effective amount of somatostatin; or a somatostatin agonist; or H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub> wherein a disulfide bond exists between the free thiols of the two Cys residues.

25 34. A pharmaceutical composition as claimed in claim 33 having the features identified in any one of claims 3 to 10 and 23 to 26.

35. Use of a somatostatin, or a somatostatin agonist; or H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub> wherein a disulfide bond exists between the free thiols of the two Cys residues, in the formulation of a 5 pharmaceutical or cosmetic composition for use in reducing excessive body weight in a human or mammalian animal.

36. Use of a somatostatin, or a somatostatin agonist according to claim 35, wherein said somatostatin 10 or somatostatin agonist has the relevant features identified in any one of claims 3 to 10 and 23 to 26.

37. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.

Docket No.  
00537/161002

# Declaration and Power of Attorney For Patent Application

## English Language Declaration



As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

### **SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING BODY WEIGHT**

the specification of which

(check one)

is attached hereto.

was filed on November 10, 1999 as United States Application No. or PCT International Application Number PCT/EP98/02999  
and was amended on \_\_\_\_\_  
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

(Number)

(Country)

(Day/Month/Year Filed)

(Number)

(Country)

(Day/Month/Year Filed)

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

08/854,941	May 13, 1997	Abandoned
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

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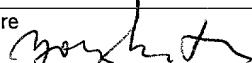
Frank R. Occhittu, Reg. No. 35,306

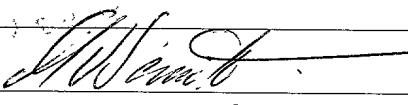
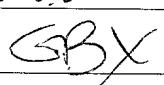
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Fifth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of sixth inventor, if any	
Sixth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

**CERTIFICATE OF MAILING BY FIRST CLASS MAIL (37 CFR 1.8)**Applicant(s): **M. A. Cawthorne et al.**

Docket No.

00537/161002

Serial No.  
**09/423,684**Filing Date  
**November 10, 1999**Examiner  
To be assigned

MAR 20 2000

Group Art Unit  
To be assigned

Invention:

**SOMATOSTATIN AND SOMATOSTATIN AGONISTS FOR DECREASING BODY WEIGHT**

I hereby certify that this An executed Declaration and Power of Attorney  
(Identify type of correspondence)  
is being deposited with the United States Postal Service as first class mail in an envelope addressed to: The  
Assistant Commissioner for Patents, Washington, D.C. 20231 on March 15, 2000  
(Date)

**Rose Lee Modano**

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04/14/2000 45-14732 00000000000000000000000000000000  
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